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Seasonal and SARS-CoV-2 pandemic changes in the incidence of gestational diabetes

Matthew Cauldwell^{1**}Yolande van-de-L'Isle¹, Ingrid Watt Coote¹, Philip J Steer²

1. Department of Obstetrics, Maternal Medicine Service, St George's University Hospital, Blackshaw Road, London, SW17 0QT
2. Academic Department of Obstetrics and Gynaecology, Chelsea and Westminster Hospital, 369 Fulham Road, London, SW10 9NH, United Kingdom

** Corresponding author: Matthew.cauldwell@nhs.net, Maternal Medicine Services, Department of Obstetrics, St George's University Hospital, Blackshaw Road, London, SW17 0QT , 020 8725 1924

Running Title "Significant seasonal variation with rates of GDM "

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Objective

To test the hypothesis that there is seasonal variation in the rates of gestational diabetes (GDM) diagnosed using a 2 hour oral glucose tolerance test.

Design

Monthly assessment of the percentage of women screened from 1st April 2016 to the 31st December 2020 who were diagnosed as having gestational diabetes

Setting

London Teaching Hospital

Population

28,128 women receiving antenatal care between April 1st 2016 and 31 December 2020.

Methods

Retrospective study of prospectively collected data.

Main Outcome Measures

Proportion of women screened diagnosed as having gestational diabetes.

Results

The mean (SD) percentage of women diagnosed with GDM was 14.78 (2.24) in summer (June, July, August) compared with 11.23 (1.62) in winter ($p < 0.001$), 12.13 (1.94) in spring ($p = 0.002$), and 11.88 (2.67) in autumn ($p = 0.003$). There was a highly significant positive correlation of the percentage testing positive for GDM with the mean maximum monthly temperature ($R^2 = 0.248$, $p < 0.001$). There was a statistically significant 33.8% increase in the proportion of GDM

diagnoses from June 2020 onwards, possibly related to a reduction in exercise secondary to the Covid-19 pandemic.

Conclusions

There is a 23.3% higher rate of GDM diagnoses in the warmer summer months. There has been a 33.8% rise in GDM diagnoses associated with the Covid-19 pandemic.

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Word Count 1807

Short Title “GDM rates and seasonal variation”

Introduction

Gestational diabetes (GDM) is a relatively common disorder which typically affects about one in eight pregnancies in the United Kingdom(UK)(1). A meta-analysis published in 2017 focusing on GDM diagnosed in European countries reported a prevalence of 5.4% (2). However, it should be acknowledged that many studies included in this meta-analysis are over 20 years old (3, 4). During this time maternity demographics have changed with women delaying pregnancy until they are older, there are greater rates of obesity(5) and more multiple pregnancies(6) as a result of assisted conception. All of these are known to be risk factors for gestational diabetes. At present screening for gestational diabetes in the UK is largely based on a risk factor-based approach system with guidance set out by the National Institute for Healthcare and Excellence (NICE)(7). In their guidance the gold standard for testing is a 75g oral glucose tolerance (OGTT) performed between 24-28 weeks (although testing maybe done earlier, particularly if there was GDM in a prior pregnancy). A positive result is determined by either a fasting reading of $>5.3\text{mmol/l}$ or a two-hour blood level of 7.8mmol/l . Retesting for GDM in pregnancy maybe done if there is high level of clinical suspicion despite the finding of a normal OGTT. Data from the landmark Hyperglycaemia and Adverse Pregnancy Events (HAPO) Trial only tested women using a OGTT up until 32 completed weeks of pregnancy(8), beyond this point there are concerns regarding the validity of using a OGTT to diagnose GDM and so home blood glucose monitoring is typically used.

There is increasing evidence to suggest that rates of GDM vary by season.(9). A single centre cohort study from Australia showed the prevalence of GDM was 28% higher in summer and 31% lower in winter(9). Similar findings have been replicated in several other populations. Retnakaran et al investigated beta cell function and insulin sensitivity in almost 1500 women who were screened for GDM(10). Their data showed that rising environmental temperature in the 3-4 weeks prior to testing appeared to be associated with beta cell dysfunction and therefore greater rates of GDM(10). To date there have been few studies in the UK population analysing seasonal variation in the rates of GDM(11). We there conducted a single centre study examining rates of GDM diagnosed in our institution over a 4 year period, examining the hypothesis that the rate of GDM diagnosis would be higher in the summer than in the other seasons. We also

took the opportunity of investigating the hypothesis that there had been a change in the rate of GDM diagnosis following the onset of the Covid-19 (SARS-CoV-2) pandemic.

Methods

This was a single centre study undertaken in a tertiary London hospital where there are approximately 5000 deliveries per year. Within our institution we have offered screening for GDM using a 2hr OGTT since 2010, based upon the NICE guidelines (which include ethnic/racial origin) as well as additional risk factors including a maternal age of 35 or more, multiple pregnancy, and previous late pregnancy loss. The diagnosis of GDM was initially made on either an elevated fasting plasma blood glucose level of 5.6 mmol/litre or above or a plasma glucose level of 7.8 mmol/litre or above in a blood sample taken 2 hours after a polycal drink which contains the equivalent of 75g of glucose. Data have been collected on the number of women tested and diagnosed with GDM by OGTT prospectively each month. . An update to NICE guidance in September 2015 recommended a reduction in the fasting threshold for the diagnosis of GDM to 5.3mmol/litre(7); this was implemented in our institution from 1st April 2016. We offer screening with OGTT up until 32+6 weeks' gestation; beyond this gestation we use home glucose testing. The technique used in our laboratory to measure plasma glucose is the Glucose HK Gen.3 produced by COBAS® (Roche Diagnostics). The coefficient of variation of the measurement is 0.5 – 0.7%. We have no reason to consider that the laboratory techniques used vary in their sensitivity by season.

To test the hypothesis that there is a seasonal variation in the rate of positive GDM diagnoses we examined the prevalence of GDM diagnosed by screening using OGTT only before 33 weeks' gestation to test whether there is a monthly and seasonal variation in the proportion of women tested who receive a positive result.

Because of the changes in diagnostic threshold, we have analysed only those women attending for antenatal care from 1st April 2016 until 31st December 2020. We also analysed the

demographics of women presenting for antenatal care to assess whether they showed any variation which would explain a seasonal effect.

Data were analysed using SPSS version 26. Initially we plotted the monthly proportion of screened women testing positive using an individual moving range control chart. We then plotted the distribution of that proportion against the average monthly maximum temperature at Heathrow Airport (17 miles from our institution) for which data are publically available(12). We then assessed the mean proportions diagnosed with GDM (+/- SD) by season, where winter is December to February, spring is March to May, summer is June to August and autumn (fall) is September to November inclusive. We assessed the demographics of women having their antenatal care at our institution, on the same seasonal basis. Gaussian (normally distributed) data were analysed using the Student-t test. Core outcome sets and patient involvement were not involved in this study

Results

The average proportion of women testing positive for GDM was 12.7% (SD 2.60), median 12.78 (IQR 10.68 to 13.98). Demographic data for women booked at are institution is displayed in Figure 1. Gaussian distribution was confirmed using the Kolmogorov Smirnov test. It appeared that there were higher rates of positivity in the summer months; this was confirmed on aggregated analysis by season (figure 2). The mean (SD) percentage was 14.78 (2.24) in summer compared with 11.23 (1.62) in winter ($p < 0.001$), 12.13 (1.94) in Spring ($p = 0.002$), and 11.88 (2.67) in autumn ($p = 0.003$). The average percentage of GDM diagnoses in spring, autumn and winter combined was 11.91% (SD 2.30), so the percentage was almost a quarter (23.3%) higher in the summer than in the other three seasons ($p < 0.001$).

There was a highly significant correlation of the percentage testing positive for GDM with the mean maximum monthly temperature at Heathrow Airport (figure 3), $R = 0.498$, $R^2 = 0.248$, $p < 0.001$. This effect is not associated with any significant variation in the demographics of women presenting for antenatal care by season (table 1), with the exception of the autumn, which has a

slightly younger mean age and a slightly higher proportion of South Asians compared with the other three seasons. The demographics of the summer population are not significantly different from spring or winter.

An unexpected finding was that, apart a single high proportion in July 2016, there was a consistently higher proportion of GDM positives from June 2020 onwards, following the onset of the COVID-19 pandemic. We therefore compared the six months from June to December 2020 inclusive (period 2, since the beginning of the Covid-19 pandemic) with the previous 65 months (period 1, pre-Covid). The mean proportion of GDM diagnoses in period 1 was 12.14% (SD 2.20) but in period 2 it was 16.24% (SD 2.22), $p < 0.001$, a 33.8% rise (absolute difference 4.1%). There were no significant differences in the mean age, height, weight or BMI of women booking between periods 1 and 2, nor was there a significant change in the booking proportions of white European (47.8% vs 46.7%), Black (10.7% vs 9.8%) or South Asian women (14.7% vs 13.6%), although there was a significant rise in the proportion of 'others', from 26.0% to 28.8% ($p = 0.001$).

Finally, we checked to see if there had been a change in the proportion of the bookings tested (figure 4). There was a drop in March and April 2020 due to a change in the screening policy in response to the COVID-19 pandemic, as recommended by the Royal College of Obstetricians and Gynaecologists, followed by a high value in June as the previous testing regime was reinstated, including catch-up for those not tested in March-April, following which the proportions returned to previous levels. We have reported this previously (13). However, the overall proportion tested from 1st April 2016 to May 31st 2020 (63.75% SD 7.99) was not significantly different from that during 1st June 2020 to 31st December 2020 (69.49% SD 20.5) ($p = 0.526$, unequal variances).

Discussion

Main findings

Our study demonstrates there is a significant seasonal variation with regards to women receiving a positive screening result for gestational diabetes through the OGTT, with more women being diagnosed in summer months compared to winter months. The proportion of women testing

positive is strongly correlated with the mean maximum monthly temperature. Furthermore, since the beginning of the Covid-19 pandemic there has been a significant increase in the proportion of women screened for GDM receiving a positive result.

The findings from our study in England agree with others who have examined how seasonality influences rates of GDM in (9, 14-16). In their review paper Pace and colleagues (16) report higher rates of GDM in the warmer months in Italy, Greece, Sweden, Brazil, Canada and Taiwan, although two of three studies in Australia did not (perhaps because of limited seasonal differences). The only previous study we have identified in the UK reported a GDM prevalence of 2.9% in June compared with 1.1% in November (11), but they concluded that there was no significant seasonal effect, probably because of small numbers of positive diagnoses (they only studied 4,942 women who were all white European).

Pace et al outline several different mechanistic ways in which this effect of temperature may be explained (17). One possible pathway is through brown adipose tissue metabolism. Data suggests that exposure to cold temperatures improves insulin sensitivity in those with Type 2 diabetes (18). Conversely with rising temperatures, brown adipose tissue is rather less activated(19); this may partially explain the higher rates of GDM witnessed in warmer months.

Interestingly our data did not show quite such a striking variation in rates of GDM as the Australian study by Moses et al ((9). They found that the prevalence of GDM was 29% higher in summer as compared to winter. The variation witnessed in our study was 23.3%. Whilst average seasonal temperature differences are similar in both cohorts, the mean summer temperatures they reported were much higher. There are compelling data that GDM is an important indicator that women are likely to develop Type 2 diabetes later in life, with rates being ten times greater for those with a prior history of GDM compared with healthy controls(20). Our data confirm that the rate of diagnosis of GDM is higher in the summer months, but it is not known whether this is associated with long term changes in beta cell function, or temporary changes in beta cell function and/or insulin sensitivity. It will therefore be important in future long term follow-up studies to document the season in which the GDM diagnosis was made. If diagnosis in the

summer is associated with a lower rate of long term type II diabetes, this would be in favour of the elevated rate of GDM diagnosis being due to temporary changes in insulin sensitivity rather than a permanent effect on beta cell function. Future studies should also investigate whether the season at diagnosis alters the significance of the diagnosis in relation to the clinical outcome of the affected pregnancy.

An unexpected finding was the significant increase in the proportion of women testing positive for GDM since the onset of the Covid pandemic. We hypothesise that this may be related to restricted activity during the various lockdowns(21, 22) without a commensurate reduction in dietary intake(23). A review of 11 studies of the effect of the pandemic in India (24) found that restriction of travel outside the home and workplace has led to an increase in snacking and meal frequency, paralleled by a reduction in physical activity and exercise duration, resulting in weight gain. Another study of 307 diabetics in India found an increment in mean HBA1c levels of 0.51% from a mean of 7.92% pre-lockdown to a mean of 8.43% and concluded that lockdown had produced a significant derangement of glycaemic control (25). A similar finding has been reported from Italy (26), and was attributed to “a dysfunctional adaptive reaction to lockdown-induced stress”.

Strengths and Limitations

One of the key strengths of our study is that data regarding the incidence of GDM in women screened has been collected prospectively. Although we did not record the maternal demographics specifically of those tested, we do have them for the total population, and there have been no significant temporal changes in the characteristics of the population served. We have longitudinal data spanning more than 4.5 years, with large numbers making our findings highly statistically significant. While our data are limited to a single centre and may not be generalisable to other maternity units, our cohort includes over 25,000 women; furthermore, our population is highly diverse with just over half the women booking describing their ethnicity as being something other than White European.

Conclusion

The diagnosis of GDM is significantly temperature sensitive, with the incidence being 23.3% higher in the summer months. This may affect its significance in relation to outcome, which would have management implications. There has been a significant 33.8% increase in the proportion of GDM diagnoses since the onset of the COVID-19 pandemic, which may be due to reduced exercise levels during lock down, or alternatively may be secondary to stress-induced hyperglycaemia.

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Disclosure of Interest

The authors have no disclosures of interest to report

Author Roles:

YDVL Abstraction of data and study design.

PJS analysed data and edited the manuscript

IWC – study design

MC wrote manuscript.

Ethical Approval:

Accepted Article

As this study analysed routinely collated data as part of a service evaluation ethical approval was not required.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Table 1. Demographics of women booking for pregnancy care by season

	Spring	Summer	Autumn	Winter
N (% missing)	6811 (4.2)	7078 (5.0)	7242 (3.3)	5659 (8.2)
Age (years)	32.41 (5.28)	32.29 (5.39)	31.91 (5.45)*	32.33 (5.39)
Height (m)	1.64 (0.07)	1.64 (0.07)	1.64 (0.07)	1.64 (0.07)
Weight (kg)	68.5 (14.8)	68.3 (15.0)	68.7 (15.1)	68.9 (14.9)
BMI	25.6 (5.3)	25.6 (5.4)	25.6 (5.5)	25.7 (5.3)
N (no missing cases)	7108	7447	7488	6165
White European (%)	3358 (47.2)	3528 (47.4)	3610 (48.2)	2947 (47.8)
South Asian (%)	1023 (14.4) ^a	1058 (14.2) ^b	1140 (15.2) ^{a,b}	879 (14.3)
Black African/Caribbean (%)	700 (9.8)	793 (10.6)	812 (10.8)	675 (10.9)
Other or not classified (%)	2027 (28.5)	2068 (27.8)	7685 (25.7)	1664 (27.0)

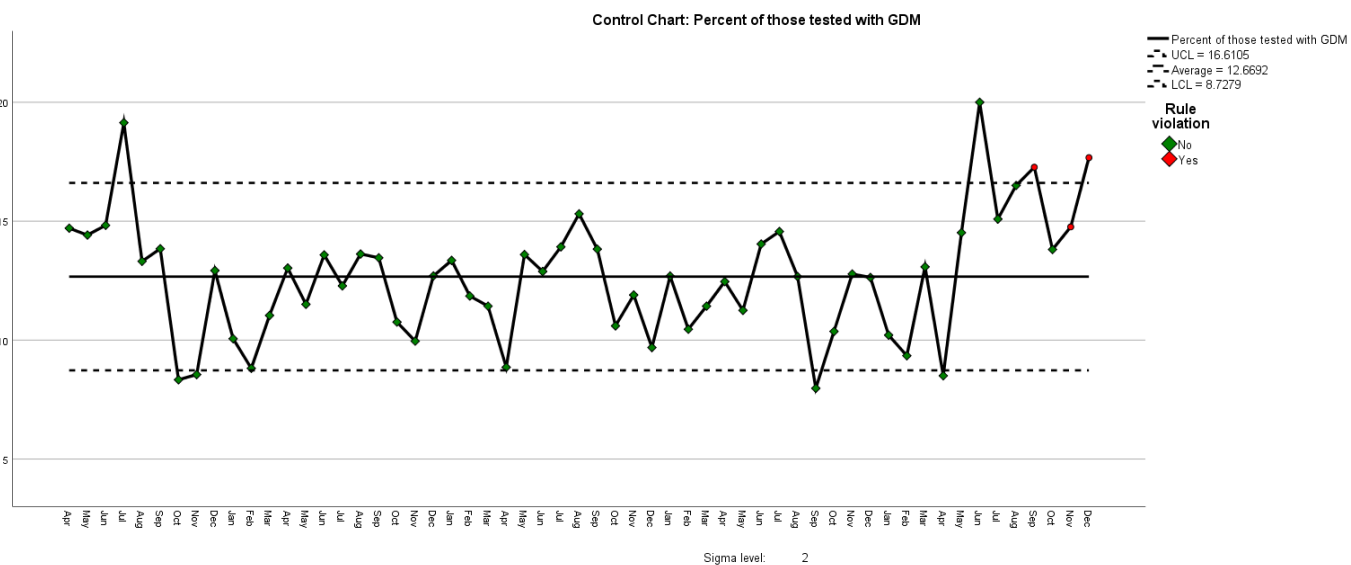
Values are mean (SD) unless otherwise stated

* $p < 0.001$ cf the other three seasons

a $p = 0.018$

b $p = 0.045$

Figure one. Control chart of proportion of women testing positive by month from 1st April 2016



Rule Violations for Run

Month	Violations for Points
Sep 2020	4 points out of the last 5 above +1 sigma
Nov 2020	4 points out of the last 5 above +1 sigma
Dec 2020	4 points out of the last 5 above +1 sigma
3 points violate control rules.	

Figure Two. Proportion of women testing positive for GDM by season

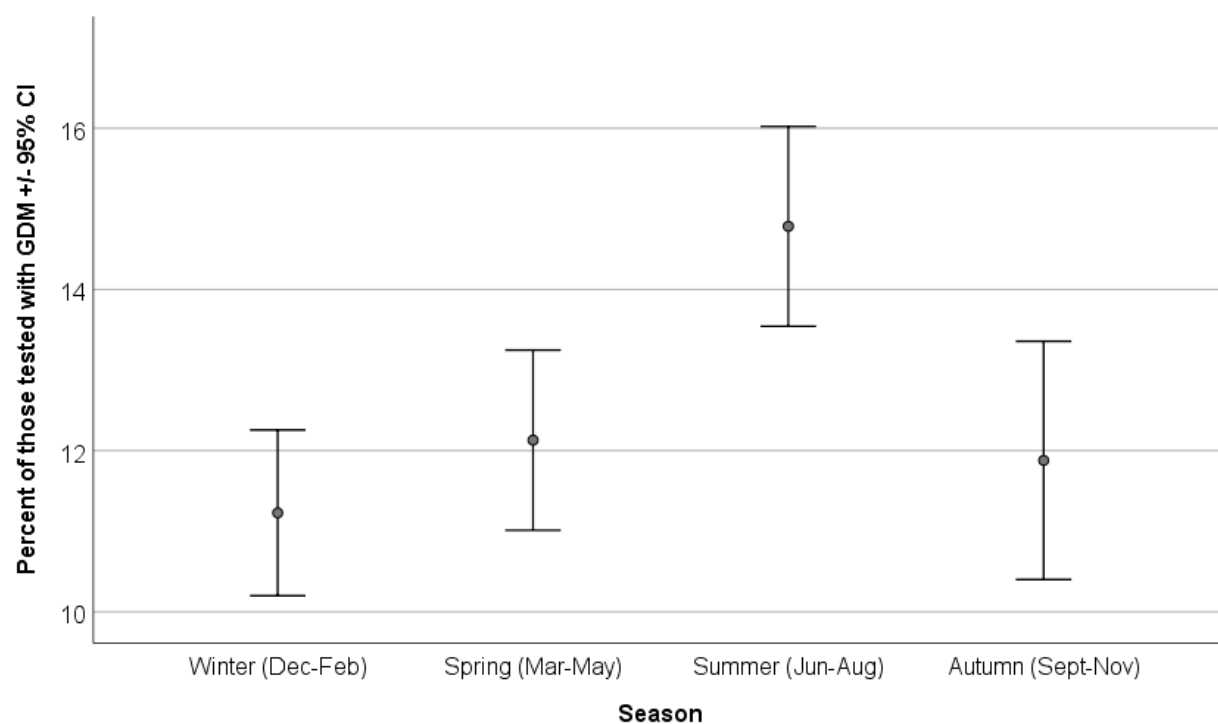
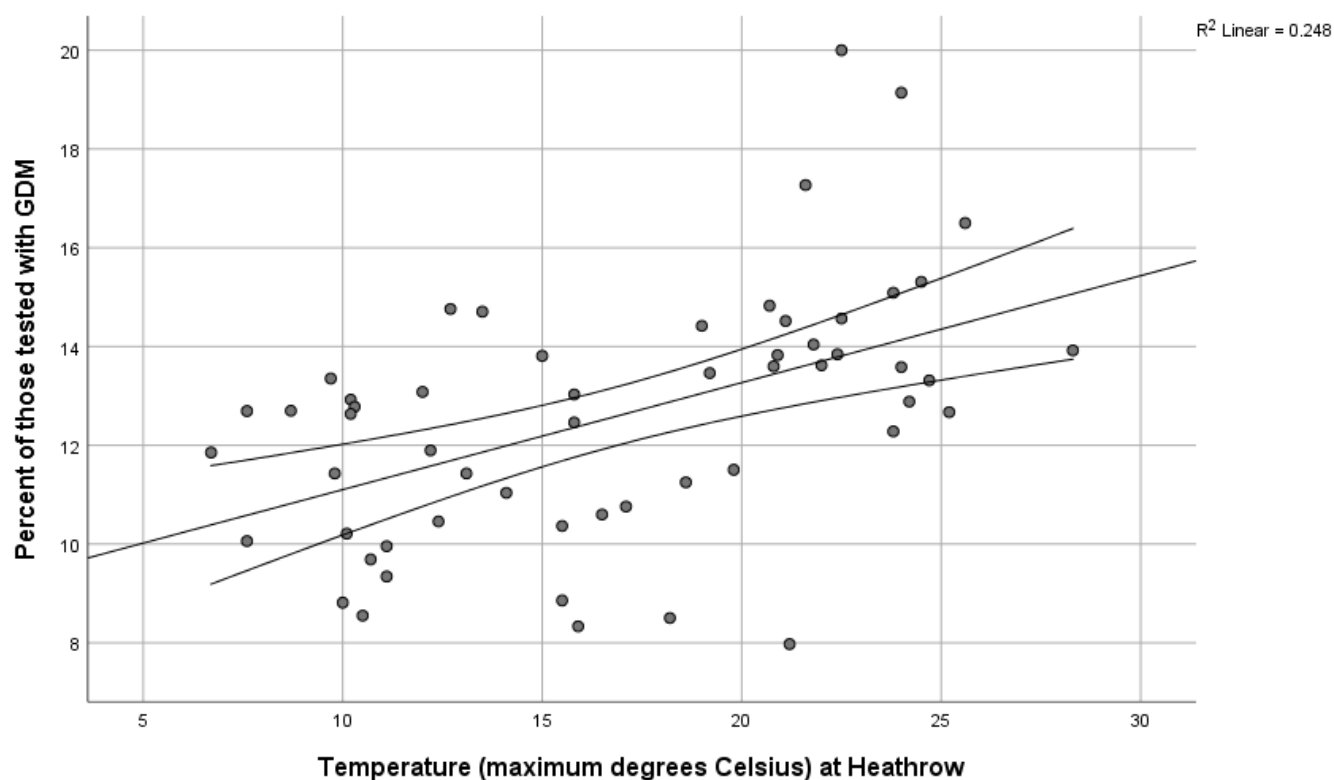
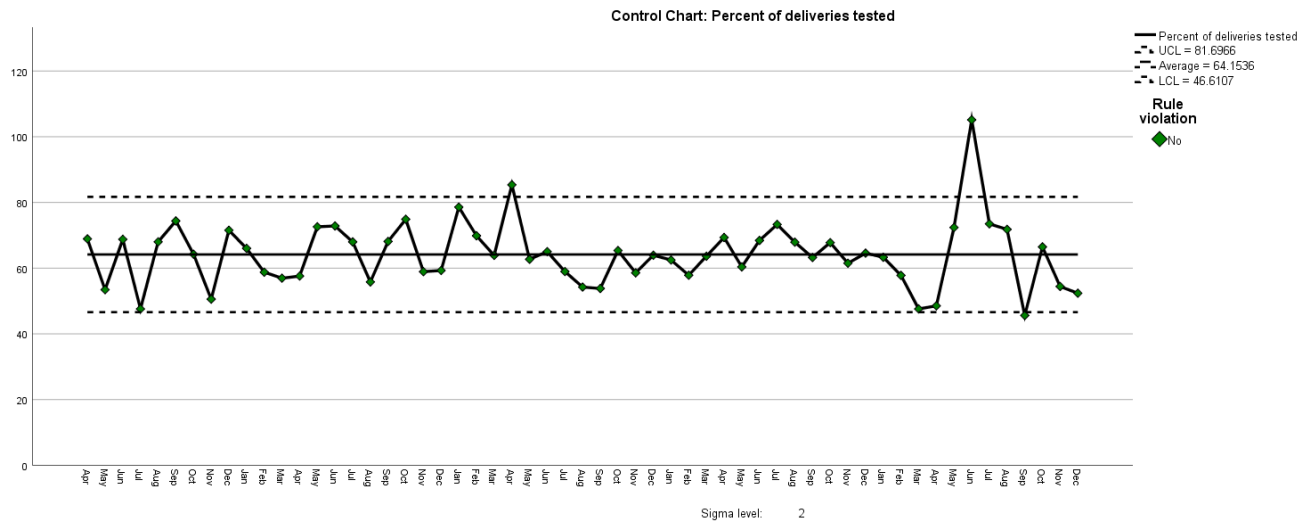


Figure Three. Relationship of percentage of women testing positive for GDM by mean maximum monthly temperature at Heathrow Airport.



Percentage of women testing positive for GDM = (temperature * 0.217) + 8.94

Figure Four. Percent of bookings tested for gestational diabetes



Rule: 4 points out of the last 5 above +1 sigma